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(FILE 'HOME' ENTERED AT 14:43:49 ON 12 MAR 2003)

FILE 'EMBASE, BIOSIS, EUROPATFULL, JAPIO, ADISCTI, ADISINSIGHT, ADISNEWS, BABS, BIOBUSINESS, BIOCOMMERCE, BIOTECHNO, CANCERLIT, CAPLUS, CBNB, CEN, CIN, CONFSCI, DGENE, DIOGENES, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, DRUGUPDATES, EMBAL, ESBIODBASE, ...' ENTERED AT 14:44:10 ON 12 MAR 2003

L1 26731 S (LYMPHOKIN? OR IL-2 OR INTERLEUKIN? OR CYTOKIN?) AND (KILLER
L2 14124 S L1 AND (EPSTEIN-BARR OR EBV)
L3 10644 S L2 AND (EPSTEIN-BARR)

=> s l1 and (il-2 or interleukin?) (50a) (killer cell or killer cells or lymphocyte?) and (epstein-barr or ebv or cmv or cytomeg? or herpes or herpes simplex)

4 FILES SEARCHED...
12 FILES SEARCHED...
24 FILES SEARCHED...
30 FILES SEARCHED...
39 FILES SEARCHED...
49 FILES SEARCHED...
64 FILES SEARCHED...

L4 7332 L1 AND (IL-2 OR INTERLEUKIN?) (50A) (KILLER CELL OR KILLER CELLS OR LYMPHOCYTE?) AND (EPSTEIN-BARR OR EBV OR CMV OR CYTOMEG ? OR HERPES OR HERPES SIMPLEX)

> s (lymphokin? or il-2 or interleukin? or cytokin?) and (killer cell or killer cells or lymphocyte?) and (epstein-barr or ebv or cmv or cytomeg? or herpes or herpes simplex)

3 FILES SEARCHED...

11 FILES SEARCHED...

16 FILES SEARCHED...

24 FILES SEARCHED...

29 FILES SEARCHED...

36 FILES SEARCHED...

44 FILES SEARCHED...

49 FILES SEARCHED...

62 FILES SEARCHED...

L1 26731 (LYMPHOKIN? OR IL-2 OR INTERLEUKIN? OR CYTOKIN?) AND (KILLER CELL OR KILLER CELLS OR LYMPHOCYTE?) AND (EPSTEIN-BARR OR EBV OR CMV OR CYTOMEG? OR HERPES OR HERPES SIMPLEX)

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L1      26731 S (LYMPHOKIN? OR IL-2 OR INTERLEUKIN? OR CYTOKIN?) AND (KILLER
L2      14124 S L1 AND (EPSTEIN-BARR OR EBV)
L3      10644 S L2 AND (EPSTEIN-BARR)
L4      7332 S L1 AND (IL-2 OR INTERLEUKIN?) (50A) (KILLER CELL OR KILLER C
L5      1665 S L4 AND (AUTOLOGOUS OR AUTO LOGUOUS)
L6      1432 S L5 AND (EPSTEIN-BARR OR EBV OR (HERPES AND SIMPLEX))
L7      183 S (LYMPHOKIN? OR IL-2 OR INTERLEUKIN? OR CYTOKIN?) AND (AUTOLOG
L8      96 DUP REM L7 (87 DUPLICATES REMOVED)
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=> s (il-2 or interleukin) (50a) (killer cell or killer cells or lymphocyte?) and (epstein-barr or ebv (herpes and simplex))

=> s (lymphokin? or il-2 or interleukin? or cytokin?) and (autologous or auto
logous) (50a) (killer cell or killer cells or lymphocyte?) and (epstein-barr or ebv
or cmv or cytomeg? or herpes or herpes simplex)

4 FILES SEARCHED...

12 FILES SEARCHED...

22 FILES SEARCHED...

30 FILES SEARCHED...

39 FILES SEARCHED...

49 FILES SEARCHED...

63 FILES SEARCHED...

L7 183 (LYMPHOKIN? OR IL-2 OR INTERLEUKIN? OR CYTOKIN?) AND (AUTOLOGOUS
OR AUTO LOGOUS) (50A) (KILLER CELL OR KILLER CELLS OR LYPHOCYTE
?) AND (EPSTEIN-BARR OR EBV OR CMV OR CYTOMEG? OR HERPES OR
HERPES SIMPLEX)

=> dup rem l7

DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, BIOCOMMERCE, DGENE,
DIOGENES, DRUGLAUNCH, DRUGMONOG2, DRUGUPDATES, FEDRIP, INVESTEXT, KOSMET,
MEDICONF, NUTRACEUT, PHAR, PHARMAML, SYNTHLINE, USAN, CHEMLIST, FOREGE, HSDB,
MSDS-CCOHS, MSDS-OHS, RTECS'.

ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L7

L8 96 DUP REM L7 (87 DUPLICATES REMOVED)

=> s (il-2 or interleukin) (50a) (killer cell or killer cells or lymphocyte?) and
(epstein-barr or ebv or (herpes and simplex))

4 FILES SEARCHED...

12 FILES SEARCHED...

27 FILES SEARCHED...

38 FILES SEARCHED...

47 FILES SEARCHED...

57 FILES SEARCHED...

L9 790 (IL-2 OR INTERLEUKIN) (50A) (KILLER CELL OR KILLER CELLS OR
LYPHOCYTE?) AND (EPSTEIN-BARR OR EBV OR (HERPES AND SIMPLEX))

=> dup rem l9

DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, BIOCOMMERCE, DGENE,
DIOGENES, DRUGLAUNCH, DRUGMONOG2, DRUGUPDATES, FEDRIP, INVESTEXT, KOSMET,
MEDICONF, NUTRACEUT, PHAR, PHARMAML, SYNTHLINE, USAN, CHEMLIST, FOREGE, HSDB,
MSDS-CCOHS, MSDS-OHS, RTECS'.

ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE

PROCESSING COMPLETED FOR L9

L10 472 DUP REM L9 (318 DUPLICATES REMOVED)

=> d 1-472

ACCESSION NUMBER: 96119657 EMBASE

DOCUMENT NUMBER: 1996119657

TITLE: Human **Epstein-Barr** virus (**EBV**)
)-specific cytotoxic T lymphocytes home preferentially to
and induce selective regressions of autologous **EBV**
-induced B cell lymphoproliferations in xenografted C.B-17
scid/scid mice.

AUTHOR: Lacerda J.F.; Ladanyi M.; Louie D.C.; Fernandez J.M.;
Papadopoulos E.B.; O'Reilly R.J.

CORPORATE SOURCE: MSKCC, 1275 York Avenue, New York, NY 10021, United States
SOURCE: Journal of Experimental Medicine, (1996) 183/3 (1215-1228).
ISSN: 0022-1007 CODEN: JEMEA

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 026 Immunology, Serology and Transplantation

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT:

C.B-17 scid/scid (severe combined immunodeficiency [SCID]) mice inoculated with
peripheral blood lymphocytes from **Epstein-Barr** virus (

EBV)-seropositive donors, or with **EBV**-transformed

lymphoblastoid B cell lines (**EBV**-LCL), develop lethal human

EBV + B cell lymphoproliferative disorders (**EBV**-LPD) with

characteristics similar to those arising in immunodeficient patients. Using

this model, we examined the capacity of human effector cells to control human

EBV -LPD. SCID mice received rabbit anti-asialo GM1 antiserum to

abrogate endogenous natural killer-cell function.

Preliminary experiments showed that adoptive transfer of peripheral blood
mononuclear cells (PBMC), purified T cells, **interleukin** (IL

) 2-activated PBMC or anti-CD3-activated T cells derived from

EBV -seropositive donors did not result in improved survival of treated

mice (in vivo effector/target ratio 2:1 to 1:1). In contrast, **EBV**

-specific cytotoxic T lymphocytes (CTL), derived from **EBV**-

seropositive donors and expanded in vitro, exhibited strong **EBV**

-specific and HLA-restricted activity both in vitro and in vivo. SCID mice

inoculated intraperitoneally with autologous but not with HLA-mismatched

EBV -LCL had significantly improved survival relative to untreated mice

after inoculation of **EBV**-specific CTL either intraperitoneally

(P<0.001) or intravenously (P<0.001) (in vivo effector/target ratio 1:1). SCID

mice bearing large subcutaneous **EBV**+ tumors and treated intravenously with 10⁷

EBV -specific CTL achieved complete tumor regression. Both CTL- and

CTL-plus-IL-2-treated mice survived significantly longer than untreated animals

or animals treated with IL-2 alone (P=0.004 and P<0.02, respectively). SCID

mice bearing two subcutaneous **EBV**+ tumors, one autologous and the

other HLA mismatched to the **EBV**-specific CTL donor, had regression of

only the autologous tumor after intravenous infusion of 10⁷ **EBV**

-specific CTL. Moreover, we could demonstrate preferential homing of

PKH26-labeled **EBV**-specific CTL to autologous but not to

HLA-mismatched **EBV**+ tumors as early as 24 h after intravenous

adoptive transfer. Immunophenotypic analyses also demonstrated preferential

infiltration of T cells into the autologous **EBV**+ tumor in SCID mice

bearing both the autologous and either fully HLA-mismatched or genotypically

related haplotype-sharing **EBV**+ tumors. The human T cells infiltrating

EBV + tumors were CD3+ and, predominantly, CD8+CD4+. Our results indicate

that **EBV**- specific CTL preferentially localize to and infiltrate

EBV+ tumors bearing the appropriate HLA antigens and thereafter induce

targeted regressions of disease.

CONTROLLED TERM: Medical Descriptors:

*cytotoxic t lymphocyte

*xenograft

*lymphoproliferative disease: TH, therapy

animal experiment
animal model
article
controlled study
effector cell
epstein barr virus
human
human cell
immune deficiency
immunophenotyping
immunotherapy
mouse
nonhuman
priority journal
scid mouse
survival
t lymphocyte activation
t lymphocyte subpopulation
tumor regression
Drug Descriptors:
*HLA antigen
*cd3 antigen
*cd4 antigen
*cd8 antigen

ACCESSION NUMBER: 2002:241363 BIOSIS

DOCUMENT NUMBER: PREV200200241363

TITLE: Infusion of autologous **Epstein-Barr** Virus (**EBV**)-specific cytotoxic T cells can treat chronic active **EBV** infection.

AUTHOR(S): Savoldo, Barbara (1); Huls, Helen M. (1); Liu, Zhengsheng (1); Volk, Hans D.; Reinke, Petra; Sabat, Robert; Babel, Nina; Jones, James F.; Gee, Adrian P. (1); Brenner, Malcolm K. (1); Heslop, Helen E. (1); Rooney, Cliona M. (1)

CORPORATE SOURCE: (1) Cell and Gene Therapy, Baylor College of Medicine, Houston, TX USA

SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 502a. <http://www.bloodjournal.org/>. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.

DOCUMENT TYPE: Conference

LANGUAGE: English

ABSTRACT:

The term chronic active **Epstein-Barr** Virus infection (CAEBV) syndrome covers a heterogeneous spectrum of **EBV**-related disorders characterized by chronic fatigue, fever, lymphadenopathy and/or hepato-splenomegaly, associated with abnormal antibody titers to **EBV**. Compared to the severe and usually fatal forms seen in Japan, in the western hemisphere this syndrome is a severely debilitating but usually non-life threatening disorder. However, current therapies with anti-viral, anti-inflammatory and steroidal drugs are often limited by severe adverse effects. Since it has been demonstrated that adoptive transfer with **EBV**-specific cytotoxic T cells (CTL) can restore **EBV**-specific immunity in immunocompromised patients, we have applied this approach to the treatment of this persistent active **EBV** infection. Using multiple stimulations with autologous lymphoblastoid cell lines (LCL) in the presence of IL-2, we have regularly been able to generate anti-**EBV** effector cells ex-vivo from a total of eight affected patients. The CTL consisted mainly of CD3+CD8+ cells which kill autologous but not HLA-mismatched LCL or a lymphokine activated natural killer cell line (mean 62% vs 9% vs 24%, at 20:1 effector: target ratio, respectively; $p < 0.001$). Moreover, the preincubation of autologous LCL with the anti-HLA class I monoclonal antibody reduced killing activity (mean inhibition 36%, $p < 0.001$). *****EBV***** -specific CTL have been infused into four patients, with 4 to 12-year histories of disease not responding to anti-viral or anti-inflammatory therapy. In all four, one to three injections of $2 \times 10^7/\text{m}^2$ of **EBV**-specific CTL resulted in normalization of the pattern of anti-**EBV** antibodies. Fatigue and malaise resolved and fever disappeared in all patients. Lymphadenopathy, present in two patients, completely regressed and the severe splenomegaly, present in one of them, was reduced from 1700 ml to 450 ml (calculated by ultrasound scan). This patient in particular was able to return to work after five years of absence, though his chronic renal failure induced by the steroid and non-steroid anti-inflammatory drugs used in the 5 years before the immunotherapy with CTL did not improve. No toxicity was observed and the clinical responses have persisted for >6 to >24 months after infusion. In addition, there was a trend for an increase in the **EBV**-CTL precursor frequency and expression of Th1-cytokines. Therefore, adoptive immunotherapy with autologous **EBV**-specific CTL may represent a safe and feasible alternative treatment for patients affected by CAEBV infection syndrome.

CONCEPT CODE: General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
Blood, Blood-Forming Organs and Body Fluids - Blood and Lymph Studies *15002
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004

Virology - Animal Host Viruses *33506
 Immunology and Immunochemistry - General; Methods *34502
 Immunology and Immunochemistry - Immunopathology, Tissue
 Immunology *34508
 Medical and Clinical Microbiology - Virology *36006
 BIOSYSTEMATIC CODE: Herpesviridae 02612
 Hominidae 86215
 INDEX TERMS: Major Concepts
 Clinical Immunology (Human Medicine, Medical Sciences);
 Infection
 INDEX TERMS: Parts, Structures, & Systems of Organisms
 CD3 positive CD8 positive cell: blood and lymphatics,
 immune system; **Epstein-Barr**
 virus-specific cytotoxic T cell [**EBV**-specific
 cytotoxic T cell]: blood and lymphatics, immune system
 INDEX TERMS: Diseases
 chronic active **Epstein-Barr** virus
 infection [chronic active **EBV** infection]:
 symptom, therapy, viral disease
 INDEX TERMS: Miscellaneous Descriptors
 lymphoblastoid cell line; Meeting Abstract; Meeting Poster
 ORGANISM: Super Taxa
 Herpesviridae: Animal Viruses, Viruses, Microorganisms;
 Hominidae: Primates, Mammalia, Vertebrata, Chordata,
 Animalia
 ORGANISM: Organism Name
Epstein-Barr virus [**EBV**]
 (Herpesviridae): pathogen; human (Hominidae): host, patient
 ORGANISM: Organism Superterms
 Animal Viruses; Animals; Chordates; Humans; Mammals;
 Microorganisms; Primates; Vertebrates; Viruses

ACCESSION NUMBER: 96:275996 NLDB
TITLE: Immunotherapy (Antiviral) "Long-Term Repopulation with
EBV-Responsive T Cells Following Adoptive Transfer of
Gene-Modified Virus-Specific T Lymphocytes." C. Li, C.Y.K.
Ng, C.A. Smith, S. Loftin, R.A. Krance, M.K. Brenner, C.M.
Rooney and H.E. Heslop. St. Jude Children's
Research Hospital, Memphis, Tennessee.
SOURCE: Gene Therapy Weekly, (17 Jun 1996) .
ISSN: 1078-2842.
PUBLISHER: Charles W Henderson
DOCUMENT TYPE: Newsletter
LANGUAGE: English
WORD COUNT: 284

TEXT:
According to an abstract submitted by the authors to the 87th Annual Meeting of
the American Association for Cancer Research, held April 20-24, 1996, in
Washington, D.C., "Adoptive transfer of antigen specific cytotoxic T cells
(CTL) is a safe and effective therapy for certain viral infections (e.g.
Lancet 1995, 345:9-13) and may prove useful in eradication of tumor
cells. Whether or not the infused T cells persist for extended periods, and
retain their ability to expand in response to antigenic stimulation is not
known. We have addressed this question by giving donor derived EBV-specific
cytotoxic T cell lines (10(7)/m(2)x4) to 19 patients following T cell depleted
BMT from a matched unrelated donor or mismatched family member. Up to 5% of the
cells were genetically marked with the neoR gene. In all patients,
administration is associated with the appearance of marker positive T cells in
the peripheral blood, and with the development of an MHC restricted anti-viral
response. The cytotoxic T lymphocyte precursor frequency rises 5 to 100 fold,
to enter the high normal range. If peripheral blood lymphocytes are cultured
with donor EBV(+) lymphoblasts, the marker gene once again becomes detectable
in both the CD4(+) and CD8(+) population. The restimulated cells retain a high
level of MHC restricted cytotoxicity against EBV(+) target cells. Evidence for
in vivo function was obtained from a patient in whom a 1000-fold rise in EBV
DNA levels in peripheral blood 18 months after CTL infusion was rapidly
followed by the reappearance of neoR positive EBV-specific T cells in the
circulation. Hence adoptive transfer of CTL leads to long-term repopulation
with cells that retain antigen specificity and expand upon challenge with the
pathogen."

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633-4931.

CONTROLLED TERM: MH Medical and Health